REMARKS

Claims 1-12 were pending in the application. Claims 1 – 3 and 5 – 12 have been cancelled by the amendments presented herein. Claim 4 has been amended. Support for the amendments to the claim can be found in the specification and claims as originally filed. Accordingly, after the amendments presented herein have been entered, claim 4 will remain pending. No new matter has been added.

Title

The Examiner has indicated that the title of the invention is not descriptive. (Office Action, p.2).

While in no way acquiescing to the validity of the Examiner's argument, and solely in the interest of expediting prosecution, Applicants have amended the title to be more clearly indicative of the invention to which the claims are directed, as indicated by the Examiner.

Oath/Declaration

The Examiner has indicated that the oath or declaration is defective because it does not identify the citizenship of each inventor. The Examiner indicates that a new oath or declaration in compliance with 37 CFR 1.67(a) is required.

A newly signed declaration in compliance with 37 CFR 1.67(a) will be forthcoming shortly.

Rejection of Claims 1 and 4 Under 35 USC 102(b)

The Examiner has rejected claims 1 and 4 under 35 USC 102(b) as being anticipated by Koch et al. (2001 Atherosclerosis). Applicants respectfully traverse this rejection.

The Examiner alleges that "Koch et al. teach a method comprising: analyzing the -819 and -592 interleukin-10 gene polymorphisms, as well as the -863 tumor necrosis

factor α gene polymorphism, determining genotype, and assessing risk of myocardial infarction." (Office Action, p.3).

The instant claim is directed to a method for diagnosing the risk of myocardial infarction, comprising the steps of analyzing two polymorphisms (1) and (2) in a nucleic acid sample: (1) polymorphism at the base number position 1019 of the connexin 37 gene; and (2) polymorphism at the base number position 242 of the NADH/NADPH oxidase p22 phox gene, (ii) determining, based on the information about said polymorphism which was obtained in the step (i), the genotype of the nucleic acid sample; and (iii) assessing, based on the genotype determined, a genetic risk of myocardial infarction.

To anticipate a claim, each and every element of the claim must be found in a single reference. This is discussed in the Manual of Patent Examining Procedure § 2131:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the . . . claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an ipsissimis verbis test, i.e., identity of terminology is not required. In re Bond, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

The Koch reference does not teach or suggest all the limitations of the instant claims. In particular, the Koch reference does not teach or suggest analyzing two polymorphisms in a nucleic acid sample: (1) polymorphism at the base number position 1019 of the connexin 37 gene; and (2) polymorphism at the base number position 242 of the NADH/NADPH oxidase p22 phox gene, as taught in the instant claims.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims 1 and 4 Under 35 USC 103(a)

The Examiner has rejected claims 1 and 4 under 35 USC 103(a) as being unpatentable over any combination of two or more of: Boerma et al. (J Int. Med. 1999), Skoog et al. (Human Mol. Gen. 1999), Inoue et al. (a) (Circulation 1998), Inoue et al. (J. Clin. Inv. 1997), (b), Lamber et al. (Human Mol. Genet. 2000), Yamada et al. (Metabolism 1998), Dammerman et al. (Proc. Natl. Acad. Sci. USA 1993), Topol et al. (Circulation 2001), or Koch et al. (Atherosclerosis 2001). Applicants respectfully traverse the rejection.

Instant claim 4 has been set forth above.

The Examiner argues that "(e)ach of these references teaches detection of at least one of the polymorphisms required in the claims as follows: Boerma et al. (position 1019 of the connexin 37 gene)...Inoue et al. (a) (position 242 of the NADH/NADPH osidase p22 phox gene)." (Office Action, p.4). The Examiner argues that "each of the references teaches that the noted polymorphism(s) are believe to be correlated with risk of myocardial infarction, or with another disease/ condition associated with the cardiovascular system." (Office Action, p.4). The Examiner argues further that "(o)ne of ordinary skill in the art would have been motivated to detect at least two, and up to all ten, of the polymorphisms taught in any combination of two or more of the cited references because this would have provided the expected and predictable advantage of additive information regarding the risk of a subject for myocardial infarction and other diseases/ conditions associated with the cardiovascular system." (Office Action, p.5). Applicants respectfully disagree.

The instant invention is directed to a method for diagnosing the risk of **myocardial infarction**. In contrast, the Boerma reference is directed to **atherosclerotic plaque** development. Accordingly, the Boerma reference uses as study subjects a borderline **hypertensive** male population, whereas the instant invention uses subjects having **myocardial infarction** (see, e.g., paragraph [0256]).

Atherosclerosis and myocardial infarction are different pathologies, characterized by different clinical features, etiologies, and treatment modalities. Although

atherosclerosis (also known as arteriosclerosis, a hardening of medium and large arteries, of which the most common form is atherosclerosis) may serve as a precursor to myocardial infarction in some cases, two additional steps of plaque rupture and thrombus formation must occur for a myocardial infarction event. Accordingly, a subject suffering from atherosclerosis does not necessarily suffer from, or may ever suffer from, a myocardial infarction. Applicants attach Appendix A which is a flow chart that depicts the relationship between arteriosclerosis and myocardial infarction. Clearly, the causes of myocardial infarction are manifold, of which arteriosclerosis is only one. It would not be clear to one of skill in the art to relate the association of the connexin 37 polymorphism in arteriosclerosis as taught by Boerma, to myocardial infarction.

Additionally, the Boerma reference does not teach or suggest detection of **any other polymorphisms** in the clinical samples tested other than the 1019 polymorphism. The Boerma reference is directed to genetic polymorphisms in connexin 37, a gap junctional protein, used as a prognostic marker for atherosclerotic plaque development. The Boerma reference describes an allelic form of the connexin 37 gene where base pair 1019 C of the coding region is overexpressed in human populations with thickening of the carotid intima, and relates this **single allelic form** of the gene to the "development of the **first single gene prognostic tool** for the identification of individuals at high risk to develop **atherosclerotic plaques**." (p.212 – 213). Boerma et al. state on p. 217 that the data presented in the study "indicate a strong and relatively unprecedented single gene allele correlation to the development of a multifactorial disease state as complex as atherosclerosis." Nowhere does the Boerma reference contemplate or suggest detecting **any other polymorphism**; rather, Boerma teach away from detecting any other polymorphism by implying that the single gene findings are "unprecedented."

The Inoue reference is directed to polymorphisms in the NADH/NADPH oxidase p22 phox gene in patients with coronary artery disease (CAD). In particular, Inoue et al. reports an association between a polymorphism of the NADH/NADPH oxidase p22 phox gene and CAD. The study described by Inoue et al. uses samples from patients all exhibiting significant coronary artery stenoses by coronary angiography (see page

135, right column). Accordingly, the study described by Inoue et al. is not directed to **one cardiovascular disease**, let alone myocardial infarction. Thus, one cannot even determine if the polymorphism described by Inoue et al. is even associated with myocardial infarction, or with another condition. Moreover, Inoue admit that the association of the polymorphism with CAD is preliminary and unconfirmed at best, and "to confirm that this polymorphism is a novel genetic marker for CAD, investigations in a larger population and other ethnic populations are necessary" (see page 137, right column).

In contrast, the instant invention is supported by the results of the large scale association study, incomparable in scale to any prior studies performed, and which provides a highly credible diagnostic outcome. Applicants refer the Examiner, for example to Figure 7 of the instant application, which is a table summarizing the backgrounds of all 5061 subjects in the relation analysis in Examples.

Specifically, the combination of the connexin 37 and the NADH/NADPH oxidase p22 phox gene polymorphisms recited in the instant invention demonstrate high odds ratios. Applicants refer the Examiner to Figure 9, which is a table showing results of multivariate logistic regression analysis of gene polymorphisms and myocardial infarction in all 5061 subjects in the relation analysis according to Examples. Referring to the Figure and described below:

(1) Odds ratios of polymorphism of connexin 37 gene (singularly): as shown in Figure 9, the odds ratio of dominant model is 1.4 (P-value is 0.0001), meaning that odds ratio is 1.4 in a case where the T allele is detected. The odds ratio of each genotype is CC 1.0, CT 1.4 and TT 1.4.

(2) Odds ratios of polymorphism of NADH/NADPH oxidase p22 phox gene (singularly): as shown in Figure 9, odds ratio of dominant model is 0.7 (P-value is 0.0027). The odds ratio is calculated as recessive model in which C allele is a risk allele, meaning the odds ratio is 1.4 (reciprocal number of 0.7) in the case where the genotype is CC. The odds ratio of each genotype is CC 1.4, CT 1.0 and TT 1.0.

(3) Odds ratios of the combination of two polymorphisms: odds ratio of a combination of polymorphisms approaches the value calculated by multiplying the odds ratios of polymorphisms. When the two polymorphisms are combined, the combination of CT or TT (polymorphism of connexin 37 gene) and CC (polymorphism of NADH/NADPH oxidase p22 phox gene) shows a maximum odds ratio whose approximate value is "1.4 x 1.4 = 1.96".

As shown above, a combination of the two polymorphisms shows a considerable association with myocardial infarction. Accordingly, analysis of the polymorphisms as described by the instant invention makes it possible to diagnose a risk of myocardial infarction with high accuracy and high predictability.

Moreover, a scientific paper which corresponds to the instant application was accepted and published in an internationally renowned journal, indicating the value of the invention and its contribution to advances in the art (Yamada Y et al. NEJM 347; 1916 – 1923, 2002).

In contrast, each of the Boerma and Inoue references teaches on its own a **single gene polymorphism** related to a cardiovascular disease; however neither reference in combination teaches or suggests all limitations of the instantly claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Conclusion

In view of the above arguments and amendments, Applicants believe the pending application is in condition for allowance. If a phone call with the Applicant's attorney would help to expedite prosecution, the Examiner is urged to contact the undersigned.

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Respectfully submitted,

By _____

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